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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,098	09/29/2003	Upender Velaparthi	LD0314 NP	2422

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EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,098	VELAPARTHI ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13,15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9* is/are allowed.

6)☒ Claim(s) *1,3-8,10-13,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/04&8/17/05&1/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election without traverse of I (and species of eg.3 in particular) in the reply filed on 8/29/06 is acknowledged.

Upon review of the claims and further consideration of the art of record as well as art newly cited, the following applies.

Claims 1,3-8,19-13,15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The variables A/B/D/E as recited are open-ended and thus unclear as to substitution thereon. Note that elected invention is directed to"C" not "C-H" or something else. There is nothing in the specification pointing to particular definition of substituents for this choice. Species are all CH when ring system is completely unsaturated. However when saturated or partially saturated nature of **remaining** group needed to fulfill valency requirements is unknown.

2. There are several claims which depend directly or indirectly on claim 2 which has been cancelled. See claims 3-8.

3. The second definition for "Z" should clearly indicate that these choices are optional substituents for "Z" choices listed directly above .The third definition for "Z" is less clear. Where are these groups being incorporated? These groups are

monovalent with the exception of the "-C(O)-" group and so their insertion into "Z" is not apparent.

4. Nature of prodrugs intended is also not known since specification is silent as to what types are suitable and at what location instant compounds should be derivatized . A prodrug is chosen based on some undesirable property present in the parent compound and once the type of improvement is identified there is testing to determine the prodrug's efficacy and ability to regenerate the parent compound. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo* . Thus the design of prodrugs is far from trivial and is dependent on the undesirable properties of the active compound(s) which will vary from drug to drug. Thus in the absence of any guidelines (none is seen in the specification) as to what type of prodrugs are suitable for instant compounds and at which locations (COOH, OH, amino groups, acyl groups) it cannot be readily determined what is and what is not within the instant scope.

5. "Such as" in claim 12 is improper alternative language since its not clear what is being claimed- subject matter before or after the term.

6. Claim 12 contains several trademark/trade name as can b seen from the "TM" designations given in the specification on p.27. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe known anticancer agents and, accordingly, the identification/description is indefinite.

Claims 6-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 6 and 7 recite sulfonyl- and sulfoxy morpholine not seen within the choices for R3 in claim 1.

Claims 1,3-8,10-13,15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Scope of quinolinones claimed are not remotely enabled as they embrace a variety of substituents in all of the R variables including "heterocyclyl" and "heteroaryl" either directly or indirectly attached to the ring systems. From a reading of the specification such a scope entails not only saturated, monocyclic rings but also bicyclic rings having any degree of unsaturation and having any number of hetero atoms in any array. In addition the functional groups can be even further substituted as described on pages 3-8. Compounds made and tested do not represent such a scope as they are always substituted with a 4-Me group on the benzimidazole portion with 5-position being piperazine either unsubstituted or substituted with acetyl, hydroxyalkyl . The quinolone portion is unsubstituted except for amino group at R6 which is always the same group, namely phenyl (hydroxyl)alkylamino. Note In re Surrey 151 USPQ 724 regarding sufficiency of

disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- The claims cover compounds easily in the billions in view of the presence of at least 10 variables coupled with the scope permitted at each as well as the possibility of partial and full saturation of quinoline ring system;

2) Level of unpredictability in the art- The invention is pharmaceutical in nature as it involves inhibition of angiogenesis- a complicated biological process which involves dealing/interfering with the presence of angiogenic activators such as VEGF in order to be successful in reaching the primary and metastatic site of a tumor. It also involves the "modulation" of other tyrosine kinase receptors of which there are many types and family members presumably by way of inhibiting a particular kinase such as EGFR and thus blocking EGFR-dependent proliferation and autophosphorylation. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. ;

3) Direction or guidance- The amount of guidance presented in the specification (on p.34) as to which compounds embraced by instant scope are sufficiently active at one or more TK receptor is not sufficient given the narrow range of compounds tested ;

4) State of the prior art- The compounds are benzimidazolyl-substituted quinolinones attached to the quinoline nucleus at the 3-position and having a variety of substituents on both ring systems. While such compounds are known in the prior art having the instant activity they there is no indication that compounds of the scope claimed will all share the necessary activity needed to practice the invention;

5) Working examples- NO actual test data has been presented only an upper range reported and no compounds particularly identified as active at one or more kinases and thus it is by no means clear how active **representative** compounds of the instant scope actually are in the absence of any structure-activity trends for the many functional groups embraced at various R variables pointed out above.

2. Scope of treating any cancer or any cancer "associated" with certain recited kinases is not enabled based on the assay tests described in the specification . The notion that tyrosine kinase inhibitors as a class can be employed for such

uses is not substantiated by the art. See for example, Burke, provided with this action, which emphasizes the lack of a clear correlation between PTK inhibition and the ability to inhibit tumor growth *in vivo*. See concluding section in the 1994 publication regarding proliferative diseases. References published after Burke such as Brower indicate research in treating cancers is still in the investigational stages and Hennequin relies on testing in animal models to determine antitumor efficacy.

Applicants' sole reliance on testing is directed to screening tests. Note Hoffman v. Klaus 9 USPQ 2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also Ex parte Powers 220 USPQ 925. In addition to the deficiency in the Wands Factors discussed above for compounds the following applies for the method claims:

Direction or Guidance: The amount of guidance presented in the specification as to which compounds are sufficiently active to be useful for a particular cancer is nonexistent;

State of the prior art: While related compound having a similar core are known as TK inhibitors, they have not been demonstrated to have the range of anticancer activity embraced herein. While there are known compounds having the

activity relied on herein in clinical trials such as SU 5416 these have different structures, namely an indolinone core, or fused pyrimidine core;

Working examples: While assay tests are described, as well as 2 cell line tests for particular cancers, no compounds have been identified as inhibiting tumor growth. In fact Carmeliet considers preclinical studies such as the type relied on by applicants as being not realistically indicative of successful cancer treatment for several reasons including the possibility that blocking one type of angiogenic molecule may not stop the tumor since tumors can switch to another type of angiogenic promoter. Also it is not clear that "most endothelial cells in tumors express the same vascular marker" or if the same marker is also present in normal tissue so additional studies are needed to confirm these assumptions. See p.255. Also in Brower it is stated on p.968 "...that certain invasive cancers can form blood vessels directly from tumor cells themselves without the need to recruit EC's."

Skill of those in the art: The prior art does not recognize any one compound as being capable of treating cancer generally. There are compounds that treat a modest range of cancers such as SU 5416 but as stated at a recent symposium on angiogenesis as synopsized in the following website:

http://www.nyas.org/ebriefreps/main.asp?intSubsectionID=3099

"The likelihood that one agent targeting any single angiogenesis mediator will become the "silver bullet" is remote." See OVERVIEW section. Thus the level of skill overall in treating cancers broadly is currently low.

In view of the above considerations, this rejection is being applied.

Claims 1,3-8,10-13,15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for salts, hydrates of compound of formulas (I) and (II), does not reasonably provide enablement for remaining scope entailed by the term. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. For scope of **solvates** there is nothing in the specification enabling such a scope which includes any organic solvent . Note Vippagunta, provided with this action, who flatly states on p.18, section 3.4 the following: "Predicting the formation of solvates or hydrates of a compound.... is complex and difficult." A **prodrug**, also included within the instant scope is chosen based on some undesirable property present in the parent compound and once the type of improvement is identified there is testing to determine the prodrug's efficacy and ability to regenerate the parent compound. No such guidance or description of suitable test(s) is seen in the specification such that one could readily determine

what is and what is not within the intended scope. Thus the design of prodrugs is far from trivial and is dependent on the undesirable properties of the active compound(s) which will vary from drug to drug. Also note that "prodrugs" by definition are not considered active agents themselves but merely compounds that will ultimately regenerate the active compounds yet method claims include such within their scope.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,3,4,6,10-13,15 and 17 are rejected under 35 U.S.C. 102(b) and (e) as being anticipated by Renhowe (WO'598 provided by applicants). Renhowe describes many compounds within the instant scope notwithstanding applicants' amendments to the claims notably at R6 for use as TK inhibitors for treating cancers. See examples such as 19-20,23,25,27,31,32,36,37,40 and 253-254 which

particularly reads on claim 3. Complex compositions are also contemplated which include any anticancer drug used in antisense and gene therapy which would include many (eg. cisplatin, 5-fluorouracil, methotrexate,etc.) if not most of those recited in claim 12.

Renhowe is applied under 102(b) since its publication date is a year earlier than applicants US filing date. It is recognized that applicants are urging benefit under 35 USC 119(e). However, benefit is not being granted in view of noncompliance with 35 USC 112, par. one for the reasons set forth in the above 112 rejections. Also see MPEP 706.02, section V, part (D).

Should applicants overcome the 112 rejections then Renhowe would be competent as of its effective filing date of 9/11/2000 which is much earlier than applicants' provisional filing date.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Renhowe (WO'598). The teachings of Renhowe as discussed in the above 102 rejection are incorporated herein. Claim 7 recites that rings including morpholino be substituted. While species exemplified by Renhowe are unsubstituted morpholino, substituents are also contemplated as can be seen in the

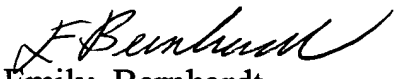
description on p.41 which relies on scope of substituents taught for "alkyl" on p.37 which includes hydroxyl, alkoxy and other groups within claim 7. Claim 8 requires that the azine rings be attached by way of an alkylene chain which is also taught. See p.42 first full paragraph. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the anticipatory compounds pointed out in the 102 rejection by adding substituents to the morpholino ring or inserting an alkylene link between azine rings such as piperazines of eg.253-254 and benzimidazole and in so doing obtain additional compounds having TK inhibitory activity in view of the equivalency teachings outlined above.

Claim 9 remains allowed as there is nothing teaching or suggesting the substitution, namely phenyl (hydroxyl)alkylamino at R6 always present in these species from the art of record or from a search in the pertinent art area.

It appears not all of applicants' IDS statements have been considered. The examiner is submitting a signed copy for IDS filed 1/23/04 and 8/17/05 and recent IDS filed 1/13/06.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



Emily Bernhardt
Primary Examiner
Art Unit 1624